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Intravenous immune globulin in chronic lymphocytic leukaemia

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SUMMARY

The most common complication of chronic lymphocytic leukaemia (CLL) is infection, which occurs mainly in advanced stages of disease or in those patients with hypogammaglobulinaemia. Intravenous immune globulin (IVIG) has been shown to be a useful prophylactic therapy against infections in such patients. A randomized, double-blind study on 36 patients receiving either 500 mg/kg or 250 mg/kg IVIG every 4 weeks was undertaken to determine the dose regimen required. There was no significant difference in the two treatment groups and we found that CLL patients were equally protected with low-dose IVIG.

Keywords chronic lymphocytic leukaemia hypogammaglobulinaemia infection immune globulin therapy

INTRODUCTION

Chronic lymphocytic leukaemia (CLL) is the most common type of leukaemia in the northern hemisphere, but it is extremely rare in the Orient. The annual incidence in the USA ranges between 1·8 and 3·0 per 100 000 population and is about 3·2 in Germany (Saarland). The incidence is age-related and increases to 30·4 per 100 000 persons between 80 and 84 years of age. CLL is very uncommon under the age of 30. It affects about twice as many men as women [1,2].

CLL is a monoclonal disorder characterized by the proliferation and accumulation of small lymphocytes of B cell (95%) or T cell (5%) lineage. Chromosomal abnormalities are detected in about 50% of patients. Most common is the trisomy 12 (31% of all abnormalities), followed by abnormalities involving 13 q (23%), 14 q (19%) and 11 q (17%), respectively [3–6].

The following diagnostic criteria were proposed by various CLL working groups [7,8]. (1) An absolute peripheral blood lymphocyte count of more than $10 \times 10^9/l$ (the National Cancer Institute working group recommended $5 \times 10^9/l$). (2) Bone marrow aspirate with more than 30% lymphocytes among all nucleated cells. (3) A majority of peripheral blood lymphocytes with B cell markers, including either κ or λ light chains, surface immunoglobulin with low surface density expression, the presence of B cell-specific differentiation antigens, such as CD19, CD20 and CD24 or CD5, in the absence of pan T cell markers.

STAGING SYSTEMS

The prognosis of CLL patients is very heterogeneous and can vary from an indolent course over years, to a more aggressive illness with death occurring within 1–2 years after diagnosis.

Different prognostic parameters have been claimed to be of importance. Lymphocytosis, lymph node enlargement, hepatomegaly and/or splenomegaly, anaemia and thrombocytopenia are the basic factors for the clinical staging system of CLL published by Rai *et al.* [9], which classifies patients into five prognostic groups. Recently Rai *et al.* simplified their classification and proposed three groups of prognostic importance [9,10] (Table 1).

A similar classification based on involved lymph node areas, anaemia (with the Hb value under 10/dl) and thrombocytopenia was established by Binet *et al.* [11,12] (Table 2). Both staging systems are widely used, Rai's classification more in

Table 1. Rai staging system

Original Rai system	Clinical and laboratory features*	Survival (months)	Modified Rai system risk group
0	Lymphocytosis only in blood and marrow	> 120	Low
I	Lymphocytosis + enlarged nodes	95	Intermediate
II	Lymphocytosis + splenomegaly and/or hepatomegaly	72	Intermediate
III	Lymphocytosis + anaemia (haemoglobin < 110 g/l)	30	High
IV	Lymphocytosis + thrombocytopenia (platelets < $100 \times 10^9/l$)	30	High

* In stages II–IV, lymph node enlargement may be present or absent; in stages III and IV, splenomegaly and hepatomegaly are not essential features.

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Table 2. Binet staging system

Stage	Clinical features	Survival* (months)
A	Haemoglobin $\geqslant 100\,g/l$, platelets $\geqslant 100 \times 10^9/l$; and < three areas involved†	> 120
B	Haemoglobin $\geqslant 100\,g/l$; platelets $\geqslant 100 \times 10^9/l$; and $\geqslant$ three areas involved	61
C	Haemoglobin $< 100/g/l$ or platelets $< 100 \times 10^9/l$ or both (independently of the areas involved)	32

* Weighted median survival was derived from eight different series that involved a total of 1117 patients.

† Five areas include the cervical, axillary and inguinal lymph nodes (whether unilateral or bilateral), the spleen and the liver.

the USA, Binet's in Europe. The International Workshop on CLL (IWCLL) recommended the adoption of an integrated Binet/Rai system.

Other parameters that have been shown to be of importance and are associated with a shorter survival time are: (1) a rapid lymphocyte doubling time, (2) a diffuse pattern of bone marrow infiltration, and (3) an abnormal karyotype. The prognostic value of other factors, such as hypogammaglobulinaemia, high serum levels of soluble CD23 and high serum deoxythymidine kinase levels, is still controversial [13–17].

The most frequent complications seen in patients with CLL are infection, thrombocytopenic bleeding and transformation of CLL into a more aggressive form (Richter's syndrome or prolymphocytic leukaemia). Infections are the cause of death in about 50% of patients [18,19]. There is a clear association between infection and hypogammaglobulinaemia, but other factors such as granulocytopenia, abnormal T cell or natural killer (NK) cell function may be of importance [20–22].

HYPOGAMMAGLOBULINAEMIA AND INFECTION IN CLL

Hypogammaglobulinaemia is more frequent in long-term survivors, in patients with diffuse bone marrow infiltration (packed marrow) and in the higher clinical stage groups (III and IV of the Rai staging system) (Tables 3 and 4).

In a recent evaluation of CLL patients diagnosed in the last 5 years (Department of Haematology, Universitätsklinik Mainz, Germany) (unpublished data) we found that a higher

Table 3. Bone marrow involvement and hypogammaglobulinaemia

Type of infiltration	*n*	Hypogammaglobulinaemia IgG < 8·0 g/l	IgG ⩾8·0 g/l
Nodular	21	3 (14%)	18 (86%)
Diffuse			
Interstitial	28	8 (28%)	20 (72%)
Packed marrow	18	15 (83%)	3 (17%)
		$P = 0{\cdot}00002$	

Table 4. IgG levels and Rai stages

Stage	*n*	IgG level < 6·0 g/l	> 6·0 g/l
Rai 0	10	0	10
Rai I + II	55	12 (22%)	43 (78%)
Rai III + IV	31	13 (42%)	18 (58%)
Σ	96	25	71
			$P = 0{\cdot}016$

value of β_2-microglobulin at the time of diagnosis correlated with a rapid development of hypogammaglobulinaemia (Table 5). Patients with IgG levels < 6 g/l at 6 months after diagnosis had significantly higher β_2-microglobulin, neopterin and sCD25 levels than patients with IgG > 6 g/l at this time. The efficiency of infection prevention was shown in a randomized, controlled, double-blind clinical trial comparing placebo with intravenous immune globulin (IVIG) (Gammagard, Baxter Healthcare Corp., Glendale, CA) 400 mg/kg body weight, every 3 weeks for 1 year in patients with B-CLL and hypogammaglobulinaemia or a history of one or more serious infections [23]. There were 41 patients in the IVIG group and 40 in the placebo group and they were well matched for age, gender, disease duration and disease stage, previous therapy, recent infection history, haematological parameters and serum IgG levels. The severity of bacterial infections was graded as serious, for infection requiring systemic antibacterial therapy, or trivial, for those requiring no therapy or at most only symptomatic or topical therapy. Viral infections were graded similarly.

The patients in the IVIG-treated group had significantly fewer bacterial infections than those in the placebo group (23 versus 42, $P = 0{\cdot}01$). In 57 patients in whom seasonal bias could be eliminated because they had completed 1 full year of study, the IVIG recipients had 14 bacterial infections compared with 36 in the recipients of placebo ($P = 0{\cdot}0001$). All septicaemia episodes occurred in stage C patients. Thirty-two stage C patients entered into the multicentre study and eight suffered from septicaemia: 5/19 in the IVIG group and 3/13 in the placebo group ($P = 0{\cdot}84$). Another interesting result of the study was that the patients who received IVIG remained free of serious bacterial infections for a longer period after entering the study than those receiving placebo treatment. No difference was seen in the incidence of viral or fungal infections.

Table 5. Predicting factors for hypogammaglobulinaemia

	Time from diagnosis to development of IgG deficiency (< 6·0 g/l) < 6 months	> 6 months	*P*
β_2-microglobulin (mg/l) ($n = 74$)	4·06 ± 2·8	2·84 ± 1·45	0·03
Female ($n = 22$)	4	18	0·02
Male ($n = 56$)	26	30	

Table 6. Incidence of infections during the study of high-dose versus low-dose IVIG

	High-dose (500 mg/kg)	Low-dose (250 mg/kg)
Bacterial	7	9
Minor	2	2
Serious	5	7
Viral	5	9
Minor	4	7
Serious	0	2
Fungal—minor	1	1
Unknown	10	3
Minor	9	1
Serious	1	2
Σ	23	22
Serious infections per patient-year	0·33	0·38

In a follow-up-study [24], 12 patients who completed the first trial continued in a cross-over, double-blind study using the same dose of IVIG and the same infusion schedule. There was no life-threatening bacterial infection in 191 3-week periods in the IVIG group, whereas nine infections occurred in 162 similar periods in the placebo group. The infections tended to occur when the serum IgG level was below normal ($< 6{\cdot}4$ g/l; $P = 0{\cdot}046$) [24].

In a multicentre study carried out in Luxembourg, Oxford (UK) and Mainz (Germany), 34 patients with B-CLL and two patients with a low-grade Non-Hodgkin's lymphoma (NHL) with IgG levels below the lower limit of normal for the local hospital laboratory, or with a recent history of one or more serious infections, received IVIG at either 500 mg/kg or 250 mg/kg body weight every 4 weeks for 1 year. There were 23 episodes of infection in 180 patient-months on study in the high-dose treatment group, and 22 in 223 patient-months in the low-dose group ($P = 0{\cdot}3$) (Table 6). Types of infections seen were similar in both studies (about two-thirds were bacterial and predominantly affected the respiratory tract). The infusions of IVIG were well tolerated and there were no serious toxic effects. The most frequent side-effects noted were chills, fever or both.

Both studies demonstrated that it was not possible to prevent infections in all B-CLL patients receiving IVIG. Although IgG levels were shown to be helpful for predicting infections (they tended to occur when the serum IgG level was below 6·4 g/l), there were also patients with low levels who did not get infections. Therefore, other factors may be of importance as indicators of infection risk, such as neutrophil count, functional ability, or the number of NK cells. The absence of specific antibodies may prove to be a more precise indication for benefit from IVIG therapy [20,25,26]. Treatment with IVIG is costly and in our study no significant difference has been seen in patients receiving high-dose and low-dose IVIG. We propose that CLL patients with IgG levels below 6 g/l and/or with a previous history of serious infections who do not have spontaneous specific anti-pneumococcal antibodies, are initially given the lower dose of immune globulin (250 mg/kg/month). This dose may be increased if breakthrough infections occur, as is common practice in patients with primary antibody deficiencies. Alternatively, IVIG replacement can be adjusted to maintain a serum IgG level above 6 g/l [27].

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